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Michal Schwartz
Jonathan Kipnis

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Multiple Sclerosis as a By-Product of the Failure to Sustain Protective Autoimmunity: A Paradigm Shift

MICHAL SCHWARTZ and JONATHAN KIPNIS

Department of Neurobiology
The Weizmann Institute of Science
Rehovot, Israel

Autoimmune diseases are traditionally viewed as an outcome of a chaotic situation in which an individual's immune system reacts against the body's own proteins. In multiple sclerosis, a disease of the white matter of the central nervous system (CNS), the immune attack is directed against myelin proteins. In this article, the authors propose a paradigm shift in the perception of autoimmune disease. They suggest that an autoimmune disease may be viewed as a by-product of the malfunctioning of a physiological autoimmune response whose purpose is protective. The proposed view is based on observations by their group suggesting that an autoimmune response is the body's own mechanism for coping with CNS damage. According to this view, all individuals are endowed with the potential ability to evoke an autoimmune response to CNS injuries. However, the inherent ability to control this response so that its beneficial effect will be expressed is limited and is correlated with the individual's inherent ability to resist autoimmune disease induction. The same autoimmune T cells are responsible for neuroprotection and for disease development. In patients with CNS trauma or neurodegenerative disorders, it might be possible to gain maximal autoimmune protection and avoid autoimmune disease induction by boosting the immune response, using myelin-associated peptides that are nonpathogenic or antigens that simulate the activities of such peptides. In patients with multiple sclerosis and other neurodegenerative diseases, where the aim is to block the autoimmune disorder while deriving the potential benefit of the autoimmune response, the effect of treatment should be immunomodulatory rather than immunosuppressive. In this article, the authors present a novel concept of protective autoimmunity and propose that autoimmune disease is a by-product of failure to sustain it. They summarize the basic findings that led them to formulate the new concept and offer an explanation for the commonly observed presence of cells and antibodies directed against self-components in healthy individuals. The therapeutic implications of the new concept and their experimental findings are discussed. *NEUROSCIENTIST* 8(5):405-413, 2002. DOI: 10.1177/107385802236966

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Multiple sclerosis (MS) is a relatively common neurological disorder associated with autoimmunity in young adults (for review, see Poser

2000). MS has long been viewed as a chronic inflammatory disease in which the patient's own immune cells mediate damage to myelin, and the resulting demyelination causes neuronal dysfunction and leads to neuronal loss (Pouly and Antel 1999; Pouly and others 2000). MS is therefore considered to be an autoimmune disease. The animal model meets the criterion, common to diseases defined as autoimmune, of transferability from diseased to naive animals by immune system components, which may be either T cells (cell-mediated, as in the case of multiple sclerosis) or antibodies (humoral-mediated), without the intervention of pathogenic microorganisms. Individuals or strains that suffer from an autoimmune disease often tend to develop other autoimmune diseases as well (Fesel and Coutinho 1998; Teuscher and others 1998).

Multiple Sclerosis—Protective Autoimmunity Gone Wrong?

The etiology of MS is uncertain (Hohlfeld and Wekerle 2001; Lucchinetti and others 2001). In patients with MS, sites of central nervous system (CNS) lesions, also known as plaques, have been found to contain T cells of different phenotypes, including CD4⁺ Th1 cells and MHC class I restricted CD8⁺ T cells. Other cells of the immune system are also present at sites of actively demyelinating plaques (Hu and others 1997; Zettl and others 1998; Muraro and others 1999; Kornek and others 2000; Huseby and others 2001; Kruger 2001). Little information is available about the identity and antigenic specificity of the cells in the demyelinat-

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Address correspondence to: Michal Schwartz, Department of Neurobiology, The Weizmann Institute of Science, 76100 Rehovot, Israel (e-mail: michal.schwartz@weizmann.ac.il).

ing plaques, as plaque biopsy is rare in MS patients. Moreover, the results of such biopsy may not clearly indicate whether the plaque is indicative of MS or a disseminated encephalomyelitis (Pouly and Antel 1999; Lassmann and others 2001).

The large variety of symptoms commonly attributed to MS probably reflects the heterogeneity of the disease (Lassmann and others 2001). At least four main kinds of demyelinating processes, each with its specific pathology, may be seen (alone or in various combinations) in patients with MS. Demyelination can be macrophage-mediated with radial expansion of the lesions, which are inflammatory infiltrates composed of T cells and macrophages. Activated macrophages and microglia are associated with myelin degeneration, attributable in part to macrophage cytotoxicity caused, for example, by tumor necrosis factor- α or reactive oxygen species (Probert and others 2000). The second type of demyelination is antibody-mediated. The lesions are similar to those seen in macrophage-mediated demyelination, with the additional deposition of immunoglobulins and activated complement at sites of active myelin destruction. The inflammation is T cell-mediated and is activated by macrophages/microglia, with complement-mediated lysis of antibody-targeted myelin. Similar lesions are found in animal models of experimental autoimmune encephalomyelitis (EAE) induced by active or passive immunization with epitopes of myelin oligodendrocyte glycoprotein (MOG). This type of demyelination is induced by T cells in combination with demyelinating anti-MOG antibodies (Linington and others 1988). The third type of demyelination is caused by distal oligodendroglial pathology. The pathology, as in the above types, is caused by encephalitogenic T cells and macrophages. Microvessel thrombosis and endothelial cell damage are detectable in these plaques. Apoptotic degeneration of distal oligodendrocytes is followed by demyelination. This type of demyelination is commonly found in virus-induced human white-matter diseases and can be seen in white

matter stroke sites (Itoyama and others 1982). The fourth type of demyelination, which is the least common in MS patients, occurs as a result of primary oligodendrocyte damage with secondary degeneration. The pathology is similar to that caused by macrophage-mediated demyelination, but there is much more degeneration of oligodendrocytes (Itoyama and others 1982).

Demyelination is thought to be responsible, at least in part, for neuronal damage (Martin and others 1992; Martin and McFarland 1995; Merrill and Scolding 1999). Studies in vitro and in vivo have shown that certain macrophage-derived substances, such as nitric oxide, glutamate, and proteases, are toxic to neurons (Martin and others 1992; Martin and McFarland 1995). Oligodendrocytes are a source of neurotrophic factors for axons, and their elimination may therefore be deleterious to neurons. It has long been thought that inflammation at the site of injury causes neuronal destruction and that the severity of inflammation will determine the extent of demyelination and further axonal death (Alcazar and others 2000). This belief, although almost universally held, has never been proved or refuted as it cannot be put to the test in human subjects. It is an assumption that applies not only to MS but also to traumatic injuries of the CNS. Accumulation of immune cells after CNS insult or in neurodegenerative disorders was long believed to be the cause of spread of degeneration. The studies summarized below suggest, however, that the presence of immune cells in the vicinity of CNS lesions is not necessarily destructive and may even have a beneficial effect in helping the injured CNS to cope with stressful conditions.

Protective Immunity

The first shift in our perception of the immune system's function in relation to the CNS had to do with the possible role of macrophages in promoting nerve regeneration (Lazarov-Spiegler and others 1996; Lazarov-Spiegler and others 1998a, 1998b; Lazarov-Spiegler and others

1999; Rapalino and others 1998). The well-known function of macrophages is to facilitate tissue repair by clearing injured tissues of dead cells, cell debris, and potential growth inhibitors, and providing the necessary growth factors for tissue regrowth. Following the demonstration in our earlier work that properly activated macrophages can promote re-growth of CNS axons (provided that certain obstacles are overcome), our entire attitude to immune system activity in the injured CNS underwent a sea change (Lazarov-Spiegler and others 1998a; Rapalino and others 1998). Once we were ready to accept the possibility that immune invasion of damaged nerves does not necessarily signify a failure of control but might—if well controlled—have a beneficial purpose, the work with T cells was started in our laboratory.

Three years ago, our research group demonstrated that T cells accumulate at the site of axonal injury (Hirschberg and others 1998), whereas almost no T cells are seen in uninjured nerves. The amount of T cells that accumulate in axotomized nerves of the CNS (optic nerves) was found to be significantly smaller than in axotomized peripheral nerves. However, when optic nerve crush was immediately followed by a systemic injection of T cells of any specificity, the accumulation was significantly increased (Moalem and others 1999b). The results of the earlier studies with macrophages encouraged us to consider the possibility that the increased accumulation of T cells, signifying increased activity of the immune system, was not merely an inevitable (and potentially harmful) side effect of the CNS insult, but a purposeful phenomenon of beneficial intent (Moalem and others 1999a). Using the established rat model of a partially injured optic nerve (Yoles and others 1992), we examined the effect of systemic injection of T cells specific to myelin self-proteins on the injury-induced spread of degeneration (secondary degeneration) known to occur, in the absence of any intervention, long after infliction of the insult (Hovda and others 1991; Katayama and oth-

ers 1991; Yoshino and others 1991; Yoles and others 1992; Faden 1993a, 1993b; Shimizu and others 1993). Survival of retinal ganglion cells in that model was significantly increased when T cells specific to myelin basic protein (MBP) were systemically injected into the injured rat (Moalem and others 1999a; Moalem and others 2000). Similar findings were obtained using a rat model of spinal cord contusive injury, where the observed neuroprotection was confirmed by morphological, anatomic, magnetic resonance imaging and functional criteria (Hauben and others 2000; Hauben and others 2001; Nevo and others 2001). Thus, the spontaneous recovery after incomplete spinal cord injury was significantly better in rats that were treated with T cells specific to MBP than in untreated injured controls (Figs. 1, 2). In seeking a physiological explanation for the finding that these encephalitogenic T cells can have a beneficial effect on the damaged CNS, we attempted to determine whether the observed neuroprotection occurs only as a result of the experimental manipulation or can be evoked spontaneously by an insult. Further results from our laboratory strongly suggested that protective autoimmunity is a physiologically evoked mechanism whereby the body harnesses the immune system in order to protect itself against neuronal degeneration (Schwartz and Kipnis 2001; Yoles and others 2001). To the best of our knowledge, this was the first presentation of evidence indicating that autoimmunity is a purposeful response of beneficial intent. In subsequent studies, we showed that splenocytes withdrawn from spinally injured rodents can provide protection when transferred to freshly injured animals (Yoles and others 2001).

Having demonstrated that a protective autoimmune response can be evoked spontaneously, we proceeded to investigate whether all individuals are capable of exhibiting such protective autoimmunity, and if so, whether this response is elicited by CNS insults of all types. Also of interest was the identity of the relevant antigen or antigens. Our recent

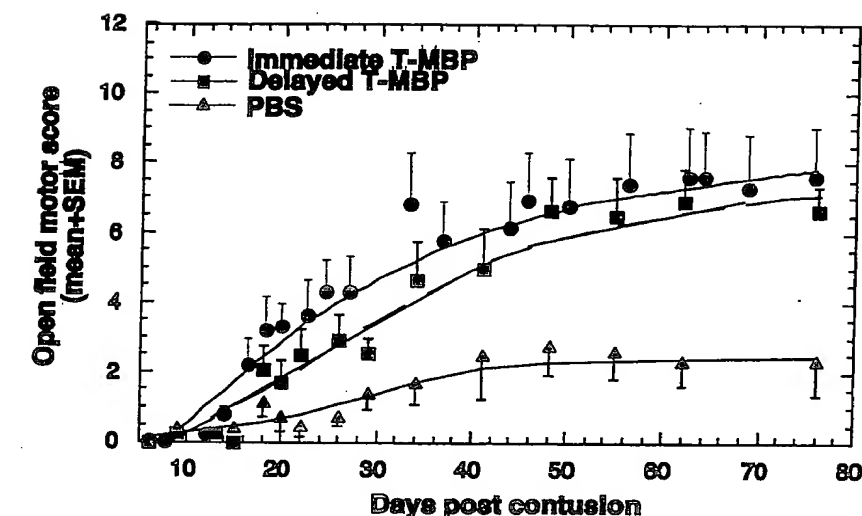


Fig. 1. Spinal cord recovery following delayed administration of anti-MBP T cells. One week after contusion at the level of T7, rats ($n = 15$) were randomly divided into two groups for injection with either PBS ($n = 8$) or 10^6 anti-MBP T cells ($n = 7$). The graph shows the mean locomotor activity scores \pm SEM at the indicated periods after T7 contusion. Plateau values reached by the anti-MBP T cell-treated rats were significantly higher than those reached by the controls ($P < 0.001$, ANOVA). For comparison, a similar experiment using six rats treated immediately with anti-MBP T cells is also shown here. There was no difference between the immediate and the delayed T-cell treatment in terms of the maximal plateau values. Taken from Hauben and others (2000). MBP = myelin basic protein.

results indicate that the ability to manifest beneficial autoimmunity is positively correlated with the genetically conferred resistance to development of autoimmune diseases (Kipnis and others 2001). This was demonstrated by the finding that when rats of resistant strains are devoid of endogenous T cells (for example, as a result of neonatal thymectomy, or due to a genetic defect as in nude mice), their recovery from CNS insults is worse than that in normal rats of the same strain (Fig. 3). These and other results led us to suggest that the beneficial response to self exists, at least potentially, in all individuals and strains but is spontaneously expressed only in those that are genetically resistant to autoimmune disease development. This correlation was found not only in models of traumatic injury of the optic nerve but also after biochemical insults caused, for example, by glutamate toxicity (Kipnis and others 2001; Schori and others 2001, 2002a, 2002b).

What makes the autoimmune response beneficial in some individuals and not in others? In particular, is it the type or the antigenic speci-

ficity of the T cells displaying the anti-self response? Our results suggest that the same types of T cells (Th1) are both potentially destructive and potentially protective (Kipnis and others 2002a). They further suggest that expression of the autoimmune response as protective or destructive depends on its regulation, which favors protection in strains that are genetically equipped to spontaneously manifest protective autoimmunity (Kipnis and others 2002b).

Is the Regulation That Is Needed for Avoidance of Autoimmune Disease Related to the Regulation Needed for Protective Autoimmunity?

Our results disclosed an inverse relationship between the susceptibility of an individual to develop an autoimmune disease and the ability to spontaneously manifest protective autoimmunity (Kipnis and others 2001). Taken at face value, this finding might indicate a) a commonality between the regulatory mechanisms of these two phenomena or b) the presence of destructive autoimmunity in

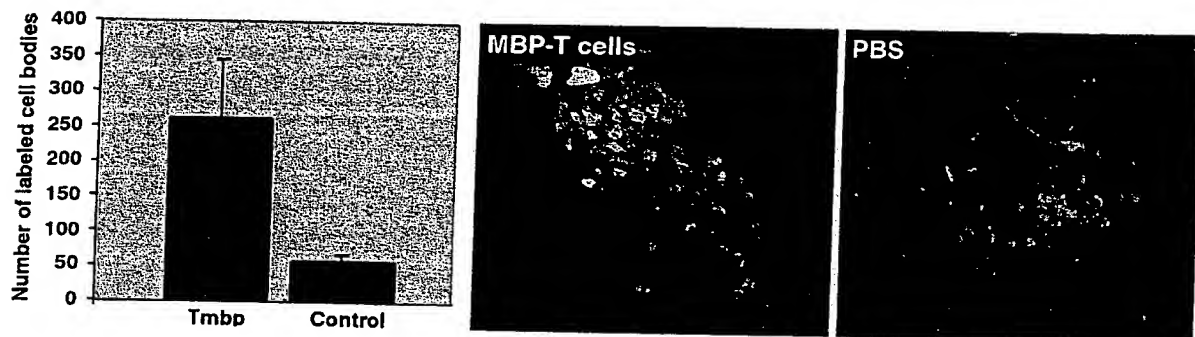


Fig. 2. Retrograde labeling of cell bodies in the red nucleus. Three months after spinal contusion at the level of T9 followed immediately by immunization with anti-MBP T cells or injection of PBS, three rats from each group were re-anesthetized and the dye rhodamine dextran amine (FluoroRuby) was applied below the site of contusion. Sections taken through the red nucleus were inspected and analyzed qualitatively and quantitatively by fluorescence and confocal microscopy. Significantly more labeled red nuclei were seen in the rats treated with anti-MBP T cells than in the PBS-treated rats ($P = 0.046$; Student's *t*-test, with correction for thickness and size of neurons). The bar graph shows the average of the total numbers of labeled red nuclei per brain. The bar graph shows the mean values \pm SD. Taken from Hauben and others (2001).

susceptible strains and its absence in resistant strains or c) the presence of protective autoimmunity in resistant strains and its absence in susceptible strains or d) the existence of more than one regulatory mechanism, with the outcome in each case probably depending on the timing of their onset.

Early attempts to understand how individuals are protected from an autoimmune response (viewed as an attack against self) yielded the proposal that anti-self T cells are deleted in the thymus during ontogeny in general. Today we know that autoimmune T cells in the periphery in individuals that are susceptible and individuals that are resistant to autoimmune diseases probably does not reflect an escape from selection. Autoreactive T cells are primed in the thymus and then released to the periphery. Myelin-specific proteins are now known to be expressed in the thymus (Fritz and Kalvakolanu 1995; Heath and others 1998; Voskuhl 1998; Liu and others 2001).

Seddon and Mason recently proposed a new theory, which postulates a third function of the thymus, namely, the production of regulatory T cells (which they named CD4+/CD25+ cells) that exist in the periphery and maintain the autoimmune T cells in a state of tolerance (Seddon and Mason 2000). The regulatory T cells, unlike the antigen-specific CD4+ cells, have a high affinity for their specific antigen and proliferate

even when the amounts they encounter are low (Shevach 2000; Stephens and Mason 2000; Mason 2001; Shevach and others 2001; Stephens and others 2001). After proliferating, the regulatory T cells become transiently noninhibitory to the potentially active CD4+ autoimmune T cells (Jordan and others 2001). According to this view, it is feasible to propose that beneficial expression of the injury-evoked autoimmune T cell response depends on the achievement of an appropriate balance between the autoimmune T cells (the potentially encephalitogenic CD4+ cells) and the regulatory T cells (high-affinity, antigen-specific CD4+/CD25+ cells). This interpretation might explain the presence of a spontaneous protective response in resistant strains and its absence or weakness in T cell-deficient individuals, as well as the corollary that in the latter, recovery from CNS injury is significantly worse than in normal individuals (Fig. 4) (Kipnis and others 2001).

Our results have shown that protective autoimmunity can be induced even in individuals (or strains) whose ability to manifest it spontaneously is limited. Thus, protective autoimmunity can be boosted in all individuals, whether well-endowed or limited in their ability to exhibit it spontaneously (Hauben and others 2001). Likewise, an autoimmune disease can develop, at least transiently, even in resistant individuals if the num-

bers of (encephalitogenic) autoimmune T cells are increased without an appropriate proportional increase in the regulatory T cells for example by passive transfer of encephalitogenic T cells or suitable activation of any other means of regulation.

We propose that the regulation of autoimmunity is a naturally occurring mechanism that serves as a safety device, allowing the injured individual to benefit from a protective autoimmunity without the risk of developing an autoimmune disease. Individuals inherently lacking this mechanism, though they cannot control the spontaneously evoked autoimmune response to injury so as to render it beneficial, can allow such protection to be induced by suitable passive or active immunization (Kipnis and others 2002a).

Multiple Sclerosis as a Special Case of a Malfunctioning Autoimmunity

The results of our studies have led us to a new view of the etiology of MS. We suggest that autoimmune T cells will be activated as the primary arm of a beneficial autoimmune response to any kind of CNS mini-trauma. In individuals who are resistant to the development of MS, meaning that they are genetically endowed with an appropriate autoimmune response, the tissue will be protected and secondary degeneration arrested. In an individual who is genetically suscep-

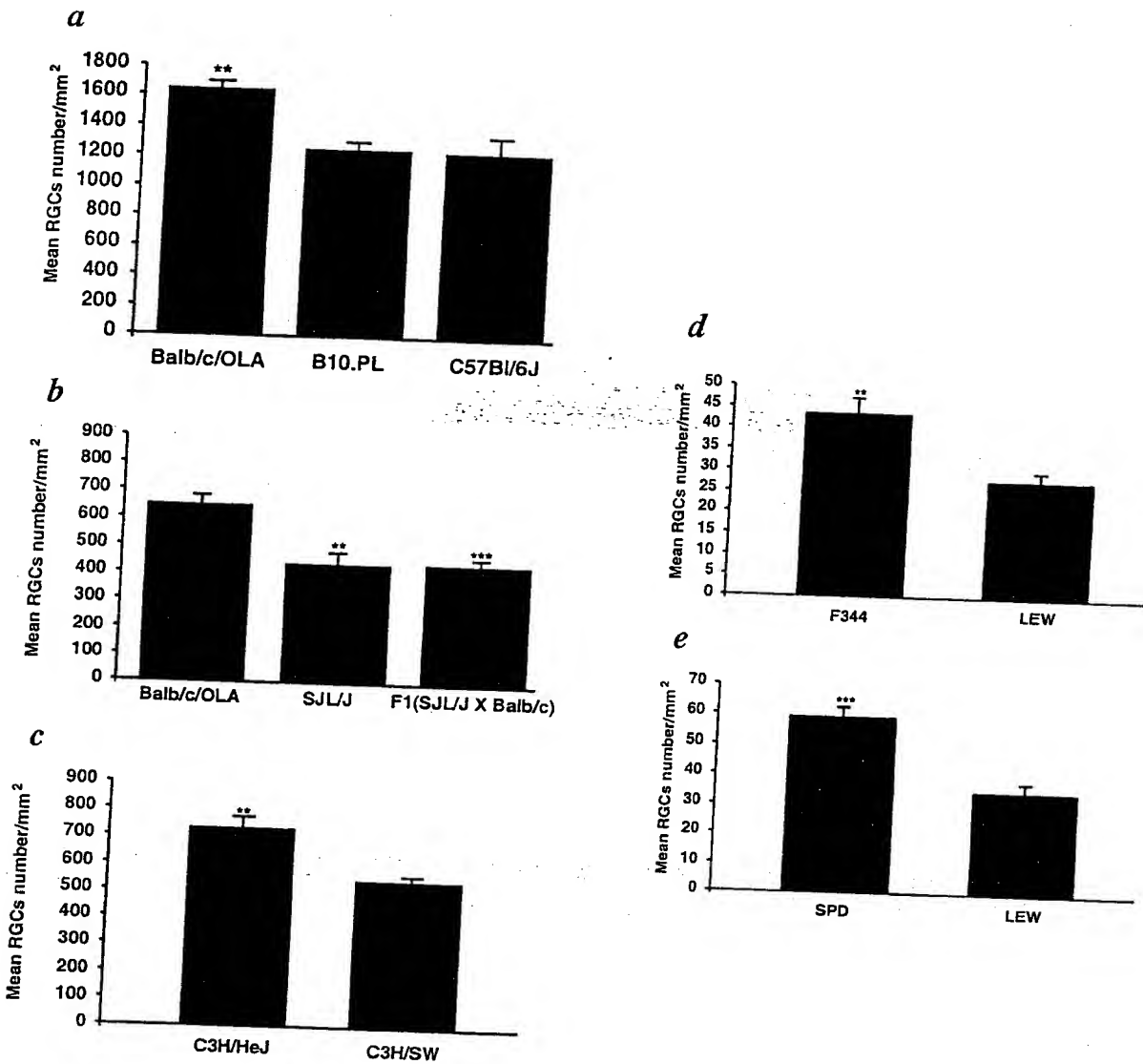


Fig. 3. Survival rate of retinal ganglion cells after optic nerve injury is associated with resistance to the autoimmune disease experimental autoimmune encephalomyelitis. The retinal ganglion cells (RGCs) of adult (a) Balb/c, B.10PL, and C57Bl/6; (b) Balb/c, SJL, F1(SJL×Balb/c); and (c) C3H/SW and C3H/HeJ mice were retrogradely labeled with the neurotracer dye FluoroGold injected stereotactically into the superior colliculus. Three days later, the mice were subjected to severe crush injury of the intraorbital portion of the optic nerve. Two weeks after injury to the optic nerve, the retina was detached from the eye, prepared as a flattened whole mount, and examined for labeled RGCs by fluorescence microscopy. Survival rates were significantly lower in SJL, C57Bl/6, B/10PL mice ($P < 0.01$) and F1 (SJL×Balb/c) mice ($P < 0.001$) than in resistant Balb/c mice. Significantly greater endogenous neuroprotection was found in C3H/HeJ mice (EAE-resistant) than in EAE-susceptible congenic mice ($P < 0.001$). The average numbers of RGCs on the uninjured side were similar (approximately 3500 RGCs/mm²) in all mouse strains. The optic nerves of adult Lewis (LEW), SPD, and Fisher (F344) rats were subjected to a partial crush injury 1–2 mm from the eye, using calibrated cross-action forceps. Two weeks later, the optic nerves were exposed for the second time and a fluorescent dye, 4-Di-10-Asp, was applied distally to the injury site. Five days after dye application, the retinas were detached from the eyes and prepared for fluorescence microscopy. The amount of endogenous neuroprotection was significantly greater in F344 (d) and SPD (e) rats ($P < 0.01$ and $P < 0.001$, respectively), known to be resistant to EAE induction, than in LEW rats, known to be susceptible to EAE induction. Taken from Kipnis and others (2001).

tible to the development of MS, these low-level traumas or infection with viruses (such as Theiler's murine encephalomyelitis virus) will have a different outcome. As in resistant individuals, they will activate an

autoimmune T cell response. This response might not be evoked in time in the susceptible strain. Once it is evoked, however, the regulation needed for its shut-off is also missing. The scenario outlined above probably

applies to injuries in general, not only injuries in the CNS. Lack or unresponsiveness of the regulatory network will cause uncontrolled immune activity, with deleterious consequences for the targeted tissue.

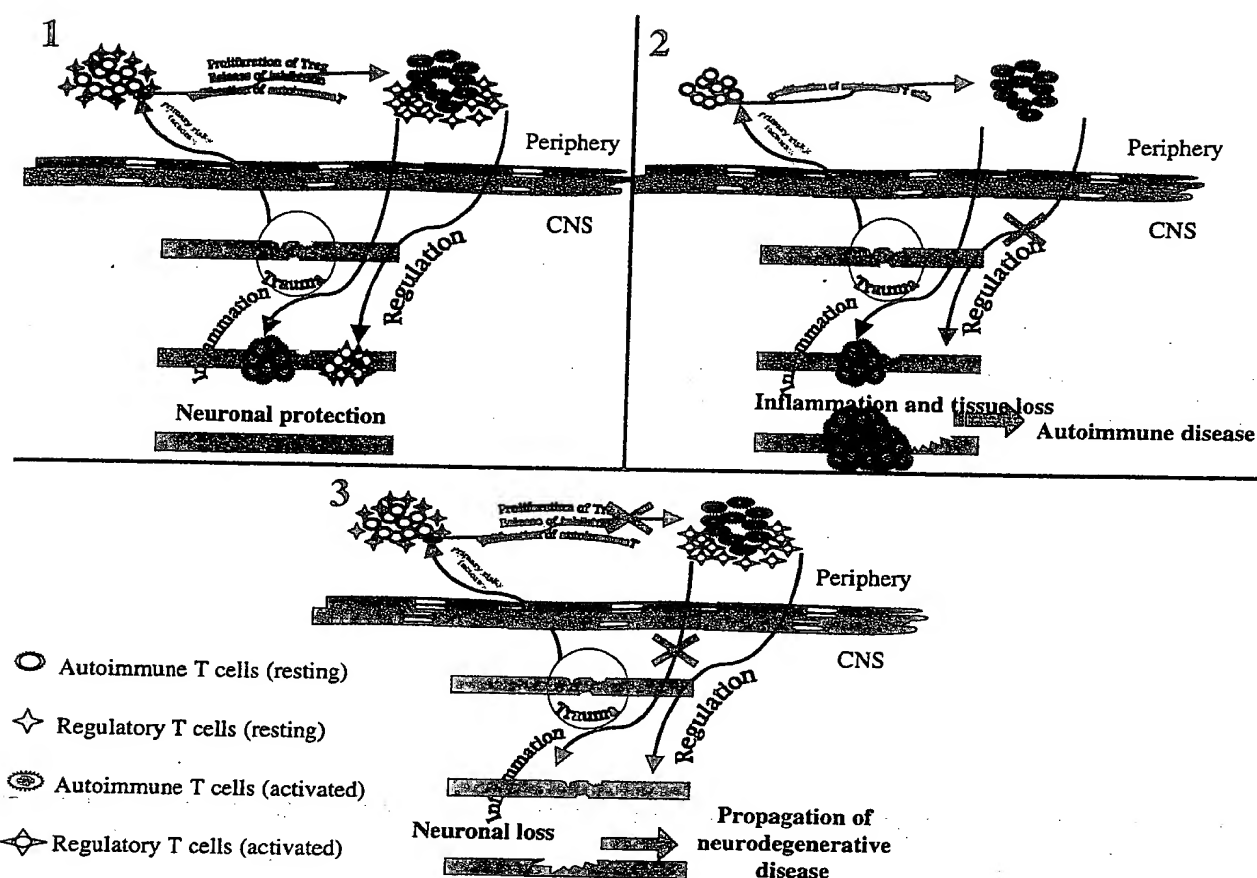


Fig. 4. Schematic illustration of injury-induced autoimmunity of beneficial intent. Central nervous system (CNS) mini-traumas of unknown etiology trigger the defense mechanisms of the immune system. Signals from the injured CNS activate regulatory T cells, causing them to proliferate. Proliferation of these cells releases their inhibitory effect on autoimmune T cells, which in turn proliferate, enter the CNS, and accumulate at the site of the injury. There they exert a neuroprotective effect, provided that they are suitably regulated by regulatory T cells. The net outcome of this well-regulated autoimmune response is the protection of neuronal tissue (1). If the regulatory mechanism is malfunctioning or missing, meaning that accumulation of autoimmune T cells (inflammation) at the site of injury is not followed by the proper activity of regulatory T cells (2), the beneficial effect of the autoimmune T cells is transient because their optimal level is exceeded and their prolonged presence at the site of injury becomes harmful. The uncontrolled accumulation of autoimmune T cells at the site of the lesion may promote tissue damage, with resulting development of an "autoimmune" disease. If the control exerted by the regulatory T cells is too stringent (3), the autoimmune T cells will be unable to proliferate at the injury site and there will be no immune reaction. The result will be tissue degeneration induced by both primary and secondary factors.

Indeed, we have results showing that the naturally occurring regulatory T cells (CD4⁺CD25⁺) are the cells whose presence limits the spontaneous autoimmunity: which in resistant strains is beneficial and in susceptible strains is either nonexistent or even destructive.

In light of the above, we propose that neuronal dysfunction associated with autoimmunity is not a direct outcome of the presence of autoimmune T cells in the CNS. Damage to the CNS evokes an autoimmune response for beneficial purposes, but it may fail to promote neuroprotection. Thus, when autoimmune T cells

arrive at the site of CNS injury, their purpose is not to mediate neuronal damage, but rather to provide help (though they may be unable to do so). The question then arises: can the ensuing syndrome be termed an autoimmune disease? Does autoimmunity cause the disease or is it a case of autoimmunity being recruited to help at the site of damage but failing to do so? In patients with HIV-induced immune deficiency, the body becomes exposed to a variety of pathogens owing to malfunction of the immune response (Innocenzi 2001; Pardo and others 2001; Szczech 2001). AIDS is defined not

as a disease originating in the immune system but as an immune system disease of viral origin. We suggest that a similar definition could be applied to MS. Damage to the CNS, caused by mini-traumas or by external pathogens, triggers the recruitment of autoimmune T cells (and, in the latter case, also anti-pathogen T cells) to the site of the lesion. The autoimmune T cells are recruited to help the nerve protect itself from the toxic effects of nerve-derived self-destructive compounds, an inevitable consequence of any primary insult in the CNS. If these T cells fail to achieve their protective

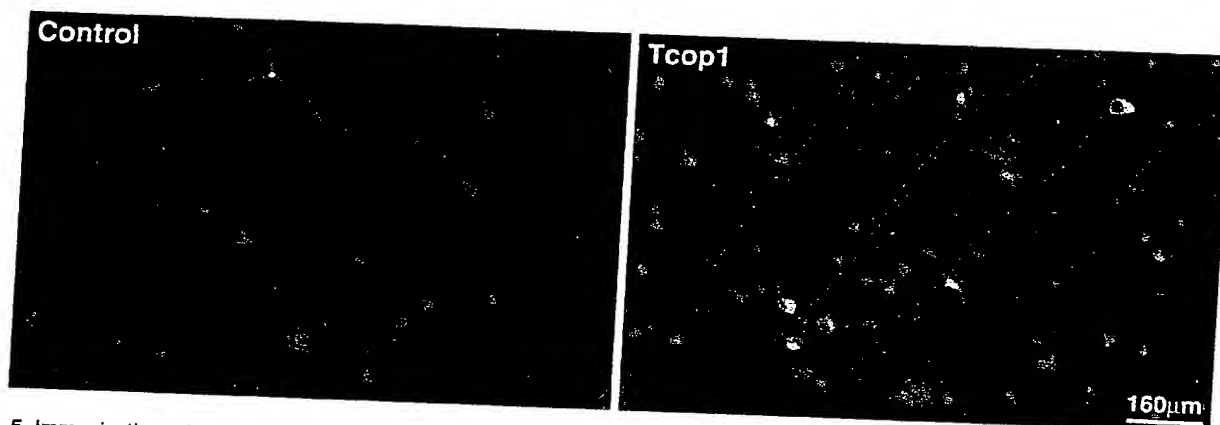
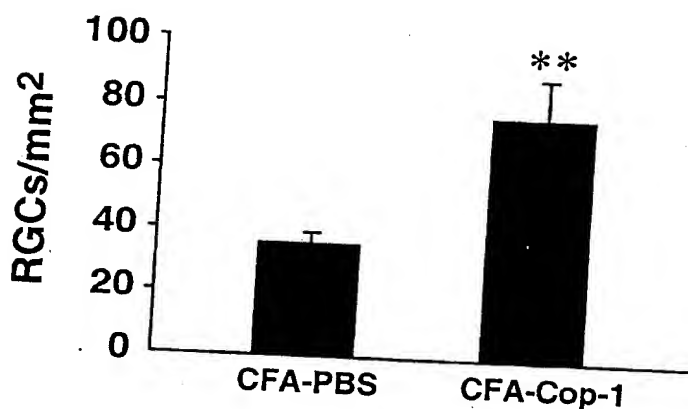


Fig. 5. Immunization with Cop-1 for neuroprotection after optic nerve injury. Lewis (LEW) rats were immunized with 250 µg of Cop-1 or with PBS emulsified in Complete Freund's Adjuvant (CFA) immediately after being subjected to crush of their optic nerve. Immunized rats showed significant neuroprotection of neuronal fibers (a) ($P < 0.05$, Student's *t*-test) relative to that of PBS-injected controls. Representative micrographs of retinas from treated and control animals are shown (b). Taken from Kipnis and others (2000). RGC = retinal ganglion cells.

mission because of the lack of regulatory T cells, the damage caused by self-destructive compounds spreads. Thus, whereas the offending pathogens are probably eliminated by the pathogen-specific T cells of the immune system, leaving no memory trace, the autoimmune T cells, having failed to exert neuroprotection, might turn destructive, causing an autoimmune syndrome. When autoimmunity is functioning properly, those mini-traumas or viral infections may not even reach our threshold of awareness, meaning that we remain oblivious to the fact that we are being protected by a beneficial

autoimmune response. It is only when the regulatory mechanism is malfunctioning that we become all too aware of the unhappy consequences of protective autoimmunity gone wrong.

Therapy for Autoimmune Disease: A Paradigm Shift

The perception of autoimmunity as the body's protective mechanism, at least in the CNS, and of autoimmune disease as a failure of protective autoimmunity, calls for a different therapeutic strategy for both autoimmune disease and CNS damage of

nonimmune character. For the treatment of autoimmune diseases, our findings argue in favor of therapy based on immunomodulation rather than immunosuppression, with the object of maximizing the beneficial component rather than eliminating the effect altogether. For the treatment of CNS damage not caused by immune dysfunction, we suggest boosting the protective mechanism (Schwartz and others 1999a, 1999b, 1999c; Schwartz and Kipnis 2001).

We recently demonstrated that immunization with a myelin-associated peptide, modified to evoke a T cell-mediated response without the

risk of inducing EAE, was beneficial in cases of optic nerve or spinal cord injury in rats (Fisher and others 2001; Hauben and others 2001). In the latter case, this strategy led to the rescue of neurons from degeneration and thus to significantly better recovery. Similarly, in cases of acute or chronic damage to the rat optic nerve, the rate of retinal ganglion cell survival was improved by vaccination with Cop-1 (Fig. 5), a synthetic copolymer that is an FDA-approved drug for the treatment of MS (Kipnis and others 2000; Schori and others 2001). Cop-1 is partially cross-reactive with myelin antigens and is non-encephalitogenic (Arnon 1996). Note, however, that Cop-1 vaccination for neuroprotection, even in a chronic model, is given in a different regimen than that currently given to MS patients, suggesting its dual effect as an anti-inflammatory and neuroprotectant in cases of autoimmune diseases and neurodegenerative-free autoimmune etiology (Schwartz and Kipnis 2001). As MS is an intermingled disease of autoimmune destruction and nonimmune degeneration, the dual effect of Cop-1 might be expressed by revisiting its regimen. It is proposed that Cop-1 paucity lies in its ability to activate with low affinity a wide range of self-reacting T cells, thereby, at least for neuroprotection, autoimmunity is being boosted with no risk of activating the high affinity (the potential pathogenic) self-reacting T cells. Our recent results suggest that its beneficial effect is probably due to immunomodulation. In our view, therefore, immunosuppression as a therapeutic strategy for CNS dysfunction should be weighed with extreme caution (Bakker and others 2000; Qian and others 2000; Ibara and others, unpublished data).

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